claims 1-4 and 13. Support for claims 20-22 is found, for example, at pages 5, 6 and 8 and Examples 4-6 of the specification, and in original claims 1-4 and 13. Support for claim 23 is found, for example, in pages 4-6 and 8 and Examples 4-6 of the specification and in original claims 1, 4 and 13. Support for claim 24 is found, for example, at pages 5, 6 and 8 and Examples 4-6 of the specification and in original claims 2 and 13. Support for claim 25 is found, for example, at pages 4-6 and 8 and Examples 4-6 of the specification and in original claims 3 and 13. Support for claims 26 and 27 is found, for example, at pages 5, 6 and 8 and Examples 4-6 of the specification and in original claims 1-4 and 13. Support for claims 28-30 is found, for example, at pages 5, 6 and 8 and Examples 4-6 of the specification, and in original claims 1-4 and 13. Support for claim 31 is found, for example, in original claims 10 and 11 and in page 4 of the specification. Support for claim 32 is found, for example, in original claims 11 and 12. Support for claims 33 and 34 is found, for example in original claims 10-12. Support for claims 35-37 is found, for example, at page 5, 6 and 8, and Examples 4-6 of the specification, and in original claims 1-4 and 13.

Applicant's claims are directed to methods and compositions employing compounds which function as GLP-1 (7-36) amide agonists, including effective fragments or analogues of GLP-1 (7-36) amide or GLP-1 (7-37). The term "agonist" is understood to refer to a compound which mimics the effects of a compound. For example, in Goodman and Gilman's The Pharmacological Basis of Therapeutics, Chap. 2, p. 30 (9th ed.

1996), the term "agonist" is defined with respect to receptor-mediated regulatory compounds, as compounds that "bind to physiological receptors and mimic the effects of the endogenous regulatory compounds." Thus, by definition, GLP-1 (7-36) amide agonists, act to mimic the effects of GLP-1 (7-36) amide, which has been demonstrated to improve glycemic control in subjects with Type I diabetes mellitus (IDDM).

The specification has been amended to correct a typographical error. No new matter has been added.

1. Section 112, First Paragraph.

Claims 1-14 stand rejected under 35 U.S.C. § 112, first paragraph, allegedly "because the specification, while being enabling for the GLP-1 (7-37) or GLP-1 (7-36) amide, does not reasonably provide enablement for an effective fragment or analog of GLP-1 (7-37) and GLP-1 (7-36) amide." June 25, 1997 Office Action at page 2.

Whatever the merits of this rejection with respect to the previously pending claims, applicant submits that the current claims fully satisfy section 112, first paragraph.

There is no requirement that, to be enabling, a patent specification must disclose each and every compound covered by the claims. Nor is there a statutory requirement for working

examples. Applicant has shown that GLP-1 (7-36) amide's effects include improved glycemic control in subjects with Type I (IDDM or insulin dependent) diabetes mellitus. By definition, GLP-1 (7-36) amide agonists function to provide such effects of GLP-1 (7-36) amide. Thus, applicant believes the disclosure provided to fully support the claimed methods and compositions.

This legal principle was clearly stated by the Court of Customs and Patent Appeals in In re Angstadt, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976):

> Appellants have apparently not disclosed every catalyst which will work; they have apparently not disclosed every catalyst which will not work. The question, then, is whether in an unpredictable art, section 112 requires disclosure of a test with every species covered by a claim. To require such complete disclosure would apparently necessitate a patent application or applications with "thousands" of examples or the disclosure of "thousands" of catalysts along with information as to whether each exhibits catalytic behavior resulting in the production of hydroperoxides. More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed. A potential infringer could readily avoid "literal" infringement of such claims by merely finding another analogous catalyst complex which could be used in "forming hydroperoxides."

It is equally well established that there is no requirement for working examples. In re Robins, 166 U.S.P.Q. 552, 555 (C.C.P.A. 1970) ("[R]epresentative examples are not required by statute and are not an end in themselves. Rather, they are a means by which certain requirements of the statute can be satisfied") (emphasis in original). See also In re Borkowski, 164 U.S.P.Q. 642, 646 (C.C.P.A. 1970) ("[T]here is no magical relation between the number of representative examples and the breadth of the claims; the number and variety of examples are irrelevant if the disclosure is 'enabling' and sets forth the 'best mode contemplated.'").

Moreover, in Examples 1-6 applicant provides procedures to evaluate GLP-1 (7-36) amide agonists. Thus, one skilled in the art would be able to determine or evaluate which compounds function as GLP-1 (7-36) amide agonists.

Withdrawal of the rejection is also appropriate in light of the relevant case law. For example, in In re Fuetterer, 138 U.S.P.Q. 217 (CCPA 1963), Judge Rich reasoned that an applicant's claims should not be so restricted that they can be avoided merely by using some compound not named by the applicant in his disclosure. 138 U.S.P.Q. at 223. Applicant's claims are fully enabled, notwithstanding that other GLP-1 (7-36) amide agonist compounds now known or later developed will function in his invention. For these reasons, applicant requests that the section 112, first paragraph, rejection be reconsidered and withdrawn.

2. Section 112, Second Paragraph/Section 101.

Claims 6-9 and 14 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite based on the assertion that "the claim does not set forth any steps involved in the method/process." June 25, 1997 Office Action at page 3. Claims 6-9 and 14 also stand rejected under 35 U.S.C. § 101 on the assertion that "the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process." June 25, 1997 Office Action at page 3.

Whatever the merits of these rejections with respect to the previously pending claims, applicant submit that the new claims submitted with this response fully comply with sections 112 and 101, and, therefore ask that the rejections of claims 6-9 and 14 be withdrawn.

3. Sections 102 and 103.

Claims 1, 2 and 4-14 stand rejected under 35 U.S.C. § 102(e) as being allegedly anticipated by U.S. Patent No. 5,424,286, "as evidenced by" Gutniak et al., N. Eng. J. Med. 326:1316-1322 (1992). The Examiner states that:

> The '286 teaches the use of GLP-1 (7-36) amide peptide, to treat both Type I (i.e. IDDM) and Type II

> (i.e. NIDDM) diabetes mellitus where the rationale for using the peptide is that it decreases the need for co-administration of insulin to treat hyperglycemia and reduce the hypoglycemic effects of insulin therapy after meal related increases of blood glucose (Column 1, lines 49-68), and References Cited on the front page of patent, in particular). The '286 patent refers to the Gutniak reference cited on the front page of the patent which is titled "Antidiabetogenic Effect of Glucagon-like peptide-1 (7-36) Amide in Normal Subjects and Patients with Diabetes Mellitus." The '286 patent teaches in vivo use of the GLP-1 peptide which therefore reads on a pharmaceutical composition of the peptide.

June 25, 1997 Office Action at page 4.

Claims 1-5 stand rejected under 35 U.S.C. § 103 as being allegedly unpatentable over U.S. Patent No. 5,424,286 in view of Gutniak et al., supra. The Examiner states:

> The claimed invention differs from the prior art only by the recitation of the administration of GLP-1 (7-36) amide or GLP-1 (7-37) at a selected time prior to ingestion of a meal.
>
> However, Gutniak et al. teach the administration of GLP-1 (7-36) amide (i.e. GLIP) 30 minutes prior to the ingestion of a meal in Type I diabetics (i.e. IDDM) and Type II diabetics (i.e. NIDDM) (Figures 2 and 3 in particular).

June 25, 1997 Office Action at page 5.

a. U.S. Patent No. 5,424,286

Applicant disagrees with the Examiner's statements concerning the '286 patent. The '286 patent relates to exendin polypeptides and pharmaceutical compositions comprising them. It does not concern GLP-1. The discussion of GLP-1 (76) amide at column 1, lines 49-68 of the '286 patent is provided only to introduce the exendin invention, and the discussion relates only to the Gutniak article. That is, the '286 patent provides no data on GLP-1 peptides; it merely discusses Gutniak et al. The discussion of Gutniak et al. in the '286 patent must be read in light of the entire Gutniak, et al. article. When it is read in this manner, it is apparent that the '286 patent mischaracterizes Gutniak et al.

Gutniak et al. describes not the treatment of IDDM patients, but day-long laboratory experiments to evaluate the effects of GLIP in which patients were hooked to a machine which allowed the continuous infusion of GLIP for over 3 ½ hours into the contralateral antecubital vein at 0.75 pmol per kilogram of body weight per minute, or in clamp studies in which GLIP was constantly infused over four hours at a rate of 0.75 pmol per kilogram per minute. In analyzing their results, Gutniak et al. stated that, "Since GLP-1 (7-36) amide, the naturally occurring form in humans, is released during a meal, and after oral glucose administration and potentiates glucose-induced insulin release, this truncated form of GLP-1 may be an important incretin" (defined in Gutniak et al. as "an endocrine transmitter that is produced in the gastrointestinal tract, is released by food intake (especially of carbohydrates), and stimulates insulin secretion in the presence of plasma peptide concentrations not

exceeding those reached after meals"). Thus, they concluded only that GLP-1 (7-36) amide -- referred to as exerting a strong "insulinotrophic" (insulin-releasing) effect -- may have a role in the treatment of "some patients with diabetes," i.e., Type II patients who still retain the ability to secrete endogenous insulin. Accordingly, the statement in the '286 patent that, "[Gutniak et al.] reasoned that since GLIP is the naturally active form found in humans after a meal, this peptide may aid in glucose regulation in IDDM and NIDDM," is not accurate.

b. Gutniak et al.

The infusion experiments described in Gutniak et al. do not support a conclusion that the use of GLP-1 (7-36) amide in the treatment of Type I diabetes mellitus (IDDM) would have been obvious at the time the invention was made to one of ordinary skill in the art. Indeed, the authors own conclusions support this, for they concluded only that "GLIP has an antidiabetogenic effect, and it may therefore be useful in the treatment of patients with NIDDM [Type II diabetes mellitus]" (Gutniak et al., Abstract). They said nothing about the treatment of other diabetics.

As indicated above, Gutniak et al. reported on two types of studies involving IDDM patients: (1) Biostator experiments in which patients were connected to a closed-loop insulin-infusion system and received insulin intravenously to keep their blood glucose concentrations normal; and (2) Hyperinsulinemic-normoglycemic-clamp studies, in which blood

glucose concentration was kept constant and glucose utilization calculated.

In the Biostator experiments, if the blood glucose was above a certain level, the Biostator increased the rate of insulin infusion to maintain a constant blood glucose level. In the Type I diabetic patients attached to this machine, the infusion of GLP-1 (7-36) amide reportedly decreased the postprandial increase in the blood glucose and plasma free insulin concentrations (Gutniak et al. at page 1318, col. 2). It did not however, report the use of GLP-1 (7-36) amide for treating such patients. The infusion of GLP-1 (7-36) amide in IDDM patients on the machine was said only to lower the meal-related requirements for exogenous insulin and also to lower the calculated isoglycemic meal-related insulin requirement (Gutniak, et al. at page 1319, col. 1).

In the hyperinsulinemic-normoglycemic-clamp studies, insulin was infused at a relatively high rate (0.8 mU/kg/min), and glucose was maintained at a concentration of 4.7 nmol/L by varying the rate of infusion. Thus, if the blood glucose concentration fell below a certain level, the rate of glucose infusion was increased. In the Type I diabetic patients in these clamp studies, the infusion of GLP-1 (7-36) amide was reported to increase glucose utilization, as compared with the infusion of saline (Gutniak, et al., at page 1319, col. 1), and this was said to indicate increased insulin sensitivity.

Thus, on the one hand, the Biostator experiments indicate that a constant infusion of GLP-1 (7-36) amide led to decreased insulin. In view of this the Examiner states that GLP-1 (7-36) amide might "decrease[] the need for co-administration of insulin to treat hyperglycemia and reduce the hypoglycemic effects of insulin therapy after meal related increases of blood glucose." On the other hand, the glycemic clamp experiments indicate that a constant infusion of GLP-1 (7-36) amide led to an increased sensitivity to the glucose lowering effect of insulin. Increased sensitivity to insulin, however, might completely offset -- and could, in fact, overpower -- a reduced amount of required insulin, thus actually increasing the hypoglycemic effects of exogenous insulin. Accordingly, these results do not support a conclusion that GLP-1 (7-36) amide is per se useful in the treatment of Type I diabetes mellitus, particularly in light of the fact that people with frank Type 1 diabetes do not produce endogenous insulin because their insulin-producing beta cells have been destroyed.

As noted above, Gutniak, et al. recognized that the data disclosed did not support the use of GLP-1 (7-36) amide for the treatment of Type I diabetes mellitus (IDDM). For example, they stated in the Abstract only that GLP-1 (7-36) amide "has an antidiabetogenic effect, and it may therefore be useful in the treatment of patients with NIDDM [Type II diabetes mellitus]," and then concluded only that:

> A better treatment for patients with NIDDM [Type II diabetes mellitus] who do not respond to sulfonylurea

> therapy would be one that decreases their requirement for insulin and therefore decreased the occurrence of hypoglycemia. Our study demonstrates that at least in the short term, the administration of GLIP decreases postprandial insulin requirements and plasma insulin concentrations in patients with NIDDM. Therefore, the peptide may have a role in the treatment of some patients with diabetes.

Gutniak et al., at page 1321 (emphasis added). Thus, although Gutniak et al. states that in these laboratory infusion studies GLP-1 (7-36) amide (GLIP) decreased the meal related insulin requirement in Type I diabetes (IDDM) patients, the treatment of Type I diabetes is neither disclosed under § 102 or suggested within the meaning of § 103, and is not even mentioned in either their introduction or their conclusion.

Applicants thus request that this rejection be reconsidered and withdrawn.

c. Pharmaceutical Compositions

With respect to the Examiner's statement that the '286 patent reads on a pharmaceutical composition of GLP-1 (7-36) amide on the ground that the '286 patent teaches in vivo use of the peptide, applicant reiterates the points made above with respect to the unexpectedness of the utility of GLP-1 (7-36) amide in the treatment of Type I diabetes mellitus. Accordingly, one of ordinary skill in the art would have had no motivation to

prepare a pharmaceutical composition for the treatment of Type I diabetes.

The Examiner appears to be ignoring the preamble of the claim, which is impermissible when the preamble is necessary to give meaning to the claim and properly define the invention.

Reference to "for use in the treatment of Type 1 diabetes mellitus" appearing in the preamble of claim 10 is properly interpreted as a claim limitation. The importance of a claim preamble, like all other claim language, is interpreted using general principles of claim construction. Bell Communications Research, Inc. v. Vitalink Communications Corp., 34 U.S.P.Q.2d 1816, 1819 (Fed. Cir. 1995). In Bell Communications the Federal Circuit summarized the law on claim construction, including a discussion of construction of claim preambles. The court reiterated:

> the general principle, as well-settled as any in our patent law precedent, that a claim preamble has the import that the claim as a whole suggests for it. In other words, when the claim drafter chooses to use both the preamble and the body to define the subject matter of the claimed invention, the invention so defined, and not some other, is the one the patent protects.

34 U.S.P.Q.2d at 1820 (emphasis in original). The court concluded that, "Preamble construction thus present no deeper mystery than the broader task of claim construction, of which it is but a part." Id.

In Bell Communications, Bell had contended that definitional status should not be accorded to the phrase, "said packet including a source address and a destination address" because it appeared in the preamble. However, the court stated that the claim at issue was "plainly limited such that it literally reads only on methods that transmit packets having both source and destination addresses." 34 U.S.P.Q.2d at 1821. Similarly, applicant's claim is directed to pharmaceutic compositions that contain an amount of a glucagon-like peptide 1(7-36) amide agonist effective to treat Type I diabetes mellitus.

First, and foremost, the language of a claim defines the scope of the claimed invention. Id. Second, claims are read in light of specification. Id. Terms appearing in a preamble may be deemed limitations when they give meaning to the claim and properly define the invention. Id. at 1820. Reference in the body of claim 10 to "an effective amount" and "pharmaceutically acceptable carrier" clearly refer back to the reference "for the treatment of Type I diabetes mellitus." These descriptions go hand in hand in describing the claimed composition, and the reference to Type I diabetes is now also specified in the body of the claim.

d. Administration Prior to Ingestion of a Meal

With respect to the Examiner's statement that "Gutniak et al. teach the administration of GLP-1 (7-36) amide (i.e., GLIP) 30 minutes prior to a meal in type I diabetes (i.e., IDDM)

and Type II diabetes (i.e., NIDDM) (figures 2 and 3 in particular)," applicant notes that, although the reported experimental protocol involved intravenous infusion of GLP-1 (7-36) amide for 30 minutes prior to ingestion of a test meal and continuing for 3 more hours (see Figures 2 and 3), the treatment of Type I diabetes -- by administering GLP-1 (7-36) amide at a selected time prior to a meal -- is not disclosed or suggested by Gutniak et al. Indeed, as discussed above, Gutniak et al. does not disclose or suggest the treatment of Type I diabetes at all. Furthermore, Gutniak et al. describes only constant infusion of GLIP, not an administration for treatment.

For the reasons provided, applicant submits that the Examiner's section 102 rejection of claims 1, 2 and 14, and the Examiner's section 103 rejection of claims 1-5, are without merit, and asks that the rejections be reconsidered and withdrawn.

CONCLUSION

For the reasons set forth above, applicant believes that the pending claims are in condition for allowance and seeks early Notice thereof. If any issues or questions arise, the Examiner is encouraged to telephone the undersigned so they may be resolved promptly.

Respectfully submitted,

Dated: December 23, 1997

By _____
Bradford J. Duft
Registration No. 32,219

LYON & LYON, LLP
First Interstate World Center
633 West Fifth Street, Suite 4700
Los Angeles, CA 90071-2066
(619) 552-8400